REMARKS

Claims 1, 2, 5-9 and 14-23 are pending in the application. Claims 1, 2, 7-9 and 18-23 are rejected. Claims 5, 6 and 14-17 have been withdrawn from consideration.

Upon entry of the Amendment, claims 2, 5-6 and 14-23 will be canceled, claims 24-25 added, and claims 1, 7-9 and 24-25 will be pending.

Support for the amendment of claims 1 and 9 to recite the amino acid corresponding to lysine 42 of mouse CaMKIIα may be found in the last paragraph of page 3 of the specification.

Support for new claims 24 and 25 may be found in paragraphs F), G) and I) on page 4 of the specification.

No new matter has been added. Entry of the amendment is respectfully requested.

I. Rejection Under 35 U.S.C. §103

At page 2 of the office action, claims 1, 2, 7-9 and 18-23 are rejected as being unpatentable under 35 U.S.C. §103(a) over Elgersma (2002), Wang (2003), Hanson (1994) and Sutoo (2002).

The Examiner states that the rejection of claims 1, 2 and 7-9 has been maintained for the reasons first set forth in the office action dated July 9, 2009. The Examiner has extended the rejection to new claims 18-23, and notes that while these claims recite the specific amino acid that is modified (lysine), Hanson allegedly teaches modification of this residue.

The Examiner has stated that the "claimed knock-in animals are essentially disclosed by Wang et al with the exception of the phenotype limitation in claim 2" (page 5, office action dated July 9, 2009), that the use of the mutant of Hanson with the knock-in animals of Wang or Elgersma would have been obvious, and that the skilled artisan would have been motivated to produce the claimed knock-in animals to further knowledge on the role of CaMKIIα in memory and learning. The Examiner concludes

that "the totality of the prior art teaches the predictable generation of CaMKIIα mutants with the claimed activity."

Applicants respectfully traverse the Examiner's position for the reasons of record set forth in the Amendment filed November 9, 2009[1], and for the following additional reasons.

First, Applicants note that the scope of the claims has been narrowed herein to specify that the lysine residue in the catalytic domain of CaMKIIα (corresponding to Lys-42 of the mouse protein) is being replaced by an arginine. Thus, the claimed knock-in animals are those that have specific physical and physiological characteristics.

Second, as to the Examiner's position that all of the claimed elements were known in the prior art, Applicants respectfully assert that none of the cited documents teaches an animal expressing an inactive CaMKIIα protein that (i) has a modified residue (K42R) in the catalytic domain, (ii) has impaired kinase activity, and (iii) has maintained both calmodulin binding activity and multimerizing activity. In particular, Elgersma does not teach an inactive CaMKIIα protein that has a modified residue in the catalytic domain. Both of the proteins taught in this publication have a modified residue in the regulatory domain and not the catalytic domain (the different domains of the protein are described in Figure 1A of Hanson). While Wang appears to teach a CaMKIIα protein having a modified residue in the catalytic domain (F89G), the modification does not result in an inactive protein. The protein of Wang is only inactivated when bound by a specific inhibitor (NM-PP1). Hanson appears to teach an inactive CaMKIIα protein having a modified residue in the catalytic domain (K42M/R). However, no evidence is provided in Hanson to show that the protein has maintained its ability to multimerize with other CaMKIIα proteins. A careful reading of Hanson reveals that while the publication appears to provide data showing that the mutant CaMKIIα protein has an inactive kinase

[1] To complete the record, Applicants are submitting herewith the Yamagata Declaration and the Carpenter's Human Neuroanatomy publication, referenced in the November 9, 2009 Amendment, but not previously provided.

domain (page 945, last sentence of the paragraph bridging columns 1 and 2) and that it has calmodulin binding activity (Figure 2A-C, "calmodulin blot"), there is no experimental evidence that demonstrates the mutant protein has retained its ability to oligomerize. While Figure 1 does suggest the mutant protein can form heteromultimers with the wild-type protein (Figure 1E-F), the authors provide neither data nor discussion as to the ability of the mutant protein to form homomultimers.

Third, Applicants respectfully assert that combination of the teachings provided in the documents would not have yielded predictable results to the skilled artisan. Indeed, the skilled artisan would not have had a reasonable expectation of success in producing a knockin animal having the claimed characteristics in light of the art cited by the Examiner and the knowledge of the skilled artisan. In particular, none of the documents cited by the Examiner would have suggested to the skilled artisan that a viable transgenic animal could be produced where the CaMKIIα protein had impaired kinase activity, yet retained both calmodulin binding activity and multimerizing activity. Hanson only studied the activity of mutated CaMKIIα protein in a cell line (COS cells), a cell line that does not naturally produce the protein. Further, as discussed above, Hanson is silent as to the ability of the mutated protein to oligomerize. Wang only provides the results of studies on the *overexpression* of an active form of the CaMKIIα protein in mice. While Wang also describes inactivation of the transgenic protein upon administration of an inhibitor, the mice had an innate, non-altered version of the gene that continued to be expressed (Applicants incorporate herein the specific comments on this point set forth at pages 5-7 of the Amendment filed November 9, 2009 in this application). Wang provides no studies whatsoever on mice expressing a kinase-*inactive* version of the protein alone. As to Elgersma, this publication was limited to studies of changes to the regulatory domain through mutation of residues 305 and 306. Elgersma provides no discussion whatsoever regarding the production of an animal having an inactive CaMKIIα protein kinase, but retaining the other activities of the protein.

Thus, nothing in the art cited by the Examiner would have suggested to the skilled artisan that a viable animal could be predictably produced where the CaMKIIα protein had impaired kinase activity, yet retained both calmodulin binding activity and multimerizing activity.

Furthermore, the skilled artisan would have understood that it would be difficult to predictably produce a healthy knock-in animal expressing CaMKIIα protein having impaired kinase activity, yet retaining both calmodulin binding activity and multimerizing activity, given the knowledge in the art of transgenics. For example, in the field of biotechnology involving gene modification, it cannot be predicted whether transgenic animals can be produced that maintain their original birthrate, survival rate, and reproduction power since they may be affected in unexpected manners by genetic modification. Indeed, Kirkwood et al. (*Proc. Natl. Acad. Sci. USA*, Vol. 94, pp. 3380-3383, 1997; *see* p. 3380, left column, section "Materials and Methods", first paragraph, line 2) and Hinds et al. (*Learning & Memory* 5: 344-354, 1998; *see* p. 345, right column, section "Materials and Methods", first paragraph, lines 5-9) teach that CaMKIIα knockout mice show significantly reduced reproduction power, and that it is consequently very difficult to obtain homozygous mice by natural mating between heterozygous mice.

Such a decrease in reproductive power is completely unpredictable in the planning stage of genetically modified animal production, and is not recognized until the actual production of the animals. Therefore, it could not be predicted from the teachings of the references whether the inactive CaMKIIα knockin nonhuman animals of the present invention, which have a satisfactory birthrate, survival rate, and reproduction power, could be produced. It was therefore surprising that such animals could be produced, that also exhibit normal birthrates, survival rates, and reproduction power (as shown in Example 6 of the present specification).

Applicants also note the surprising result that the inactive CaMKIIα knockin nonhuman animals of the present invention maintain wild-type CaMKIIα protein expression levels. A large amount of CaMKIIα protein is present in the brain, and it is

particularly known to encompass 1% of all of the proteins in the hippocampus. When the expression level of such a protein present in a high concentration is significantly reduced, as a result of a genetic modification technique, for example, the induction of secondary effects such as a compensatory increase or decrease in the expression level of other related proteins is a strong possibility. In such a case, the ability to produce mice as specific disease-model animals or disease-model cells is substantially reduced.

There is well-document precedent for CaMKIIα knockin animals expressing a significantly decreased level of protein expression. For example, in two types of CaMKIIα knockin mice, i.e., T305D and TT305/306VA, described in Elgersma et al. (p. 494, right column, section "CaMKII Expression and Phosphorylation", first paragraph, lines 5-7), the expression level of CaMKIIα protein was reduced by half in both types of mice, compared to wild-type mice. In contrast, as shown in Example 5 of the present specification, the expression level of CaMKIIα protein in the brain of the inactive CaMKIIα knockin nonhuman animal (mouse) of the present invention is hardly affected. Thus, the null effect on levels of protein expression is completely unpredictable in the pre-stage of knockin nonhuman animal production, and is not recognized until the actual production of the animals. That is, it cannot be predicted from the teachings of the references that the inactive CaMKIIα knockin nonhuman animal of the present invention, which maintains the original level of CaMKIIα protein expression, can be produced.

Thus, in contrast to the Examiner's position, Applicants respectfully assert that the prior art does not teach the predictable generation of CaMKIIα mutants with the claimed activity. Further, as discussed above, the general knowledge in this field of endeavor teaches that the production of such animals would not have been predictable.

In view thereof, Applicants respectfully request reconsideration and withdrawal of this rejection.

II. Double Patenting

At page 5 of the office action, claims 20 and 23 are rejected as being substantial duplicates of claims 18 and 21, respectively, under 37 C.F.R. §1.75.

As discussed above, claims 20 and 23 are being canceled, thus making this rejection moot. In view thereof, reconsideration and withdrawal of this rejection is respectfully requested.

III. Conclusion

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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